

Medical masks versus N95 respirators for preventing COVID-19 among health care workers: A secondary analysis of findings inconsistent with prior understanding reflects the expected inferiority of medical masks.

Mark Ungrin,^{1,2,3,*} Matthew Oliver,⁴ Julia M. Wright,⁵ Jonathan Mesiano-Crookston,⁶ Malgorzata Gasperowicz,¹ David Fisman,⁷ Corinna Nielson^{1,8}

¹Faculty of Veterinary Medicine, University of Calgary, Calgary, AB, Canada

²Department of Biomedical Engineering, Schulich School of Engineering, University of Calgary, Calgary, AB, Canada

³Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada

⁴Professional Standards Advocate, Edmonton, AB, Canada

⁵Department of English, Dalhousie University, Halifax, NS, Canada

⁶Goldman Hine LLP, Toronto, ON, Canada

⁷Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

⁸SPOR Community Advocate

*Corresponding author

Email: mdungrin@ucalgary.ca (MU)

Abstract

Background

A previously published study is cited as evidence that medical masks (MM) are noninferior to N95 respirators (N95) in the prevention of COVID infections. As COVID is transmitted via infectious aerosols generated during coughing as well as routine activities such as breathing and speaking, and N95s (in contrast to MM) are designed, validated and specified in national standards to provide protection against such hazards, we re-analysed the published data to resolve this unexpected result.

Methods

Study data was extracted from the publication, and analyses pre-specified in the original study protocol but omitted from the publication were carried out. Anomalies identified in the process were subject to additional analyses for statistical significance.

Results

Prespecified analyses reverse the reported outcome, which is the product of multiple alterations to the trial that were not introduced into the registry until after publication. Methodological shortcomings include compromised randomization, with statistically significant correlation between female sex and allocation to the higher-risk arm of the trial. Trial conditions and results at unregistered trial sites in Egypt were inconsistent with – but overwhelmed findings from – sites in the registered countries, which reflected the expected inferiority of medical masks. Substantial additional sources of bias were identified. Unexpected patterns were observed in the data.

Conclusions

The results of the study do not support the claim that medical masks are noninferior to N95s for the prevention of COVID-19.

Introduction

COVID-19 is airborne,(1–3) with transmission of the SARS-CoV-2 virus mediated at both short and long range by inhalation of infectious aerosols produced in routine activities.(3,4) Evidence for airborne transmission is well-established, and includes information available very early in (and before) the pandemic demonstrating the necessity of precautions against airborne transmission,(2,5–28) highlighted by several early outbreaks most easily explained by airborne transmission and inconsistent with realistic alternative hypotheses.(29–33) While the concentration of infectious aerosols increases with proximity to a source and where ventilation is limited, airborne transmission over longer ranges is expected unless an immediate loss of pathogen viability is known to occur – and similar to closely-related SARS-CoV-1, SARS-CoV-2 was known within the first months of the pandemic to retain viability in aerosols for extended periods.(34) SARS-CoV-1 is recognized by the World Health Organization (**WHO**) as an airborne

virus,(35) consistent with its observed behaviour(36) and a clear protective effect from appropriate personal protective equipment (**PPE**).(37)

Potential exposure to infectious aerosols is a well-understood workplace hazard,(38,39) with national standards providing explicit practice guidance.(40) PPE mitigates infection risk to both the wearer and those around them, by reducing the quantity of infectious aerosols released by an infected wearer.(40) The extensive literature in this area spans decades of research covering not only the performance of individual pieces of equipment tested at the laboratory bench, but also their ability to protect users from hazards including aerosols and pathogens in the workplace.(41–53) Unlike fitted respirators, medical masks (**MM**) are unable to provide adequate protection against bioaerosol hazards as they do not provide a seal against the face, allowing aerosolized material to bypass the mask material and be inhaled by the wearer without filtration.(54) In Canada, the currently active standard is CAN/CSA-Z94.4-18, first published in 1982(55,56) and updated in 2018. It incorporates program administration and recordkeeping requirements and includes specific guidance for healthcare facilities that the minimum appropriate PPE for potential exposure to bioaerosols that may contain a pathogen such as SARS-CoV-2 is an N95 respirator.(57)

It was thus unexpected to see the publication by Loeb *et al*(58) and rapid incorporation into guidance(59,60) of a clinical trial based in Canada which claimed that medical masks provided noninferior protection to N95 respirators against COVID infection. The study reported: *“In conclusion, among health care workers who provided routine care to patients with COVID-19, the overall estimates rule out a doubling in hazard of RT-PCR–confirmed COVID-19 for medical masks when compared with HRs of RT-PCR–confirmed COVID-19 for N95 respirators.”* The lead institution subsequently released its interpretation of the study under the heading *“Surgical masks are not inferior to N95 masks for preventing the spread of COVID-19 to health-care workers”*, quoting the lead author that *“The surgical masks were not statistically less effective than N95s in preventing COVID-19 infections in health-care providers looking after patients with COVID-19”*(61) and *“there certainly was not much of a difference between the two”*.(62)

We therefore sought to reconcile these claims with the existing body of evidence.

Methods

Overview of the Loeb *et al* study

Details of the study by Loeb *et al* can be found in the original publication(58) and supplementary materials(63) including the initial and modified protocols and statistical analysis plans(64), in the initial information(65) provided to the clinical trial registry, and in subsequent modifications made during the trial(66,67) and after publication(68,69). We will briefly review relevant details below.

Prespecified protocol

The study was prospectively registered March 3rd, 2020 at www.clinicaltrials.gov as NCT04296643,(65) specifying recruitment of 576 nurses at risk of COVID exposure in the workplace in both the prospective registration(65) and the initial study protocol,(64) a number that remained unchanged in the registry throughout the duration of the trial.(65–67) While no study sites were recorded in the initial trial registration, the initial protocol prespecified 13 sites, all located in Canada. A modification to the study record on November 16th, 2020 extended the completion date to April 1st, 2021, specifying 12 sites in Canada and 1 in Israel which remained constant through all subsequent modifications.(65–69)

The study proposed to test the hypothesis that medical masks provide similar protection against COVID to fit-tested N95 respirators by assessing the impact of intermittent use in the workplace (with participants donning their assigned PPE “...when providing care to or when within three feet of a patient with any febrile respiratory illness”) on overall infection rates, without attempting to distinguish those due to non-workplace exposures.(64) The specification that the assigned mask or N95 would be worn “...when providing care for patients with febrile respiratory illness” remained current in the trial registry throughout the duration of the trial.(65–67) The initial study protocol specified that unless widespread transmission of COVID in the community ceased participants would be followed for a period of six months,(64) a period echoed in the trial registry where it remained unchanged throughout the trial.(65–67) Impacts on the safety of patients under the care of participants and reconciliation of the substitution of medical masks for the N95 respirators required under CAN/CSA-Z94.4-18(57) were not addressed.(58,63,64,70)

Prespecified statistical analysis plan

The study used a noninferiority approach(71–73), which attempts to establish whether an intervention (MM in this case) can confidently be said to be noninferior to a reference (N95), using an allowable margin for potential inferior performance (Δ) chosen by the investigators.(72) The terminology used in such studies can become complex, as the term “noninferior” has a specific technical meaning - the intervention is not worse than the reference by more than Δ - that is more nuanced and less categorical than the meaning conveyed by common usage of the phrase “not inferior”. Similarly, “not noninferior” (failure to show the intervention is not worse than the reference by more than Δ) is not the same as “inferior” (the intervention is statistically significantly worse than the reference), and it is possible for an intervention to be found simultaneously inferior and noninferior if to a statistically significant degree it performs worse than the reference intervention, but does not reach the Δ set by the investigators.(71,74) Care and attention to detail are essential in all research, but particularly critical in noninferiority trials – where “Trials to show superiority generally penalize the sloppy investigator... By contrast, non-inferiority trials tend to reward the careless. The less rigorously conducted the trial, the easier it can be to show non-inferiority.”(74) Recognition in the field of the potential for manipulation of analyses to ensure a desired finding of noninferiority via post hoc enlargement of Δ (72) makes prespecification essential for credibility.

The choice of Δ is necessarily subjective and of significant interest to those to whom study findings are applied, as it represents a quantitative declaration of the degree of potential inferiority that is accepted under a finding of noninferiority. Importantly, where risk is cumulative over time (as is the case here), the

specification of Δ is inseparable from the interval over which it is to be assessed. To give an extreme example for clarity, accepting an absolute increase in risk of an adverse event of 5% each year is vastly different from accepting the same absolute increase in risk on a daily basis.

The Δ criterion defined in the initial protocol (dated March 06, 2020)(64) was: *“If the upper 95% confidence limit around the difference between the effectiveness of the medical mask and N95 respirator is greater than a margin of 5% then the null hypothesis, that the medical mask is not non-inferior to the N95 respirator, will be accepted”*. E.g. COVID incidence in the N95 group was to be subtracted from incidence in the MM group, and if the 95% confidence interval around the point estimate of the difference included the possibility that the difference is greater than 5%, then the hypothesis that MM are not noninferior to N95 is to be accepted.

In partial compliance with the long-standing requirement to consider sex and gender in CIHR-funded research(75) and Canada’s Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2)(76) the protocol specified collection and analysis of data on participant age and sex.(64)

Analysis was pre-specified as: *“All outcomes will be analyzed on a per-protocol basis in accordance with non-inferiority study design”*.(64) Per protocol (**PP**) refers to analysis restricted to participants who complete the protocol as assigned – protocol violations such as receipt of a vaccine would result in that subject being excluded from the analysis. The complementary approach, intention to treat (**ITT**) analysis, includes assessment of all participant data, regardless of treatment actually received, withdrawal or deviation from the protocol.(77) PP analysis is considered more stringent in this context, however best-practice guidance is that a finding of noninferiority should meet the prespecified criteria under both PP and ITT approaches.(71) A review of the pitfalls of noninferiority trials(72) warned that: *“Whereas using ITT may be thought of as conservative in a superiority trial and is generally recommended, it is anti-conservative in a noninferiority trial because protocol violations will make the two arms more similar and hence reduce the chance of finding a difference between the two treatments if one exists.”* and *“Intention to-treat analyses will generally be biased toward finding no difference, which is usually the desired outcome in noninferiority and equivalence trials and is favored by studies with many dropouts and missing data.”*(72)

Protocol modifications

The number and location of the sites at which the study took place are unclear. Only 12 sites in Canada and 1 in Israel were ever recorded in the registry. However, the main text of the publication refers to 17 acute care hospitals in Canada and 2 long term care facilities in Israel,(58) while Supplement Tables 10 and 12(63) refer to 23 (which a Correction(78) subsequently increased to 24) study units in Canada with no outbreaks and 5 more that had outbreaks, plus 2 sites in Israel.

The publication also introduced data from 4 unregistered acute care hospitals in Pakistan and 6 more in Egypt,(58) although data from *“11 study units”* in Pakistan and *“6 hospital sites”* in Egypt is presented in Supplement Table 12.(63) Collected after data collection was completed in Canada and Israel, the unregistered sites accounted for the large majority of both participants (70.1%) and COVID cases (78.8%) in the trial, expanding total recruitment to 1,009. A post-publication modification to the study record on December 21st, 2022 updated enrollment to 1,009 from the target of 576 that had been specified in the

registry throughout the duration of the trial,(68) while a second modification on January 11th, 2023 introduced the first record of sites in Pakistan and Egypt, listing one location in each country.(69)

Assuming the 29 study units in Canada and 11 in Pakistan represent locations within the 17 and 4 acute care hospitals specified respectively, and that no further study sites exist that were excluded from analysis, 5 hospitals in Canada, 3 in Pakistan and 5 in Egypt remain unidentified. Recognizing we lack evidence for these assumptions, we tentatively accept them in the absence of both prespecified records and information consistent with the publication in the trial registry.

The study period was reduced from the six months specified in the initial proposal and in the registry to 12 weeks, and then to 10 weeks(58,64).

Modifications to statistical analysis plan

No analysis of sex or gender data was presented. The table of participant characteristics lists count and percentage female by country and intervention, but these data are not otherwise mentioned, and the words “sex”, “gender” or “male” do not appear in the main text or Supplementary Material.

Shortly before the trial ended on March 29, 2022, the Δ criterion was significantly enlarged, from the prespecified 5% to “*Noninferiority will be defined by a hazard ratio of < 2 at an alpha of 0.025*”, a change that first appeared in a document entitled “Statistical Analysis Plan Version 1.0 – 02-17-22” (**Fig. 1**), and was reiterated in a protocol revision provided in the supplementary materials dated March 1st, 2022.(64)

The March 2022 protocol revision also expanded analysis to “*Data will be analyzed by intention to treat and per protocol*”,(64) consistent with the requirement to demonstrate an outcome of noninferiority under both PP and ITT analyses.(71) The modifications also included the important commitment “*Regardless of vaccine, doses received, or if active follow up was < 10 weeks, we will determine for all participants whether they developed RT-PCR confirmed COVID-19 by 10 weeks.*” These data are required for ITT analysis. While receipt of a vaccine represents a protocol violation and PP analysis excludes data from such participants entirely, in ITT all data must be included in the analysis.(79,80)

These data were omitted from the publication, and what was reported as ITT analysis is better described as “modified ITT”.(81) Strictly speaking the analysis presented was neither PP nor ITT, but a hybrid of the two that included censored patients in the denominator as in ITT, but excluded all COVID cases among them from the numerator as in PP (**Fig. 2**).

The 2022 revisions also redefined “per protocol”(64) to include any subjects who completed at least 80% of the 10-week follow up. We refer to this revised definition as PP₈₀ for clarity (**Fig. 2**). Redefining a participant who does not meet PP criteria as having done so is inconsistent with the nature of PP analysis; no rationale was provided for this change. Both the prespecified PP analysis and the new PP₈₀ analysis were omitted from the publication.

Participants in receipt of vaccines were excluded from the study and censored from analysis, as were those with a previous known COVID infection, with both modifications inserted into the registry after publication.(68) An exception was made for Sinopharm and Sinovac vaccines, on the grounds that the trial team considered them to be ineffective (which they defined as efficacy below 50%).(58) No evidence

for this decision was provided, and it is inconsistent with WHO assessments of >50% efficacy for both, which were available prior to the start of enrolment in Pakistan and Egypt(82,83) and updated prior to publication of the study.(84,85) This exception only affected participants at the unregistered sites in Pakistan and Egypt (where ~75% and ~50% respectively would otherwise have been excluded).(58,68)

The exclusion on the basis of previous known COVID infection is specified in more detail in the updated study protocol dated March 01, 2022 as “*Participants known to have tested positive for COVID (by RT-PC, antibody, or antigen testing) are excluded.*” Seropositivity (a positive COVID antibody test) at baseline was ~80% or higher in Pakistan and Egypt countries (573 individuals, vs 9 in Canada and Israel), however it did not trigger the exclusions on the grounds of previous COVID infection or receipt of an effective vaccine.

Reconstruction of study data

The data sharing statement accompanying the Loeb *et al* publication limits access to a six month window, with a number of time-consuming conditions and restrictions on the types and purpose of permitted analyses. Sharing is also indicated to be conditional on the authors having completed unspecified secondary analyses, as well as an unspecified internal approval process.(58) We therefore chose to reconstruct the data reported in the publication.(58)

Custom ImageJ(86) macros were employed to convert the information from graphical to quantitative form (**Supplementary Table 1**), with reference to the “at-risk” numbers provided below each plot. Ambiguity was resolved by distributing events uniformly across available options. For example if three censor marks appear on the chart, but the at-risk numbers indicate four participants were censored during the relevant interval, each censor mark was assigned a value of 4/3. For reasons that are unclear, MM data from Israel after day 52 (comprising two of the six infections and seven censored participants) was omitted from Loeb *et al* Fig. 4 (the pale line should exit the top of the chart to indicate cumulative risk in the MM arm was off the top of the Y-axis scale). These data were reconstructed using information from Loeb *et al* Fig. 2. Minor differences were not pursued further as they are expected due to the above-noted ambiguities and do not impact subsequent analysis.

As the “at risk” values shown in Loeb *et al* Fig. 3 represent the number of participants remaining after removing those infected with COVID or censored due to vaccination, the denominator for the omitted, prespecified PP analysis may be obtained by adding the numbers from the final column to the number of cases in the corresponding arm of the study. In the MM arm, the number of participants meeting PP criteria is $(383 + 52 =) 435$; in the N95 arm it is $(390 + 47 =) 437$. PP_{80} values can be obtained in the same way, with the caveat that simply adding the “at risk” number at day 56 in Loeb *et al* Figure 3 to the total number of infections will double-count infections that occur after that day (once as infections, once as not yet infected), so it is necessary to subtract them once from the total. With four cases in the MM arm of the study after day 56, and two cases in the N95 arm, PP_{80} group sizes were therefore $(400 + 52 - 4 =) 448$ and $(408 + 47 - 2 =) 453$ respectively.

Serology data was collected for all participants, with baseline seropositivity presented in the table of participant characteristics.(58) Seroconversion data are presented in Loeb *et al* Supplement Table 2, as

are combined data for all participants with laboratory-confirmed COVID (“infection confirmed by either RT-PCR or by seroconversion”). Data for PCR-confirmed COVID cases within the subgroup of participants who were initially seronegative is presented in the Supplement Figure on the last page of the Supplementary Material.(63)

Data from the prespecified 6-month follow up period was not collected and is therefore not possible to reconstruct. However, translation of the prespecified Δ of 5% absolute increase in risk for MM over 6 months (26 weeks) to shorter periods is straightforward. Equation ① relates risk per week (R_1) to risk over W weeks (R_W):

$$\textcircled{1} \quad R_1 = 1 - (1 - R_W)^{\frac{1}{W}}$$

The initial study protocol (which appears to be taken directly from the proposal submitted for scientific review) assumes 5% infection rate in N95 wearers over 6 months ($R_{26}^{N95} = 0.05$), and prespecifies up to 10% infection ($\Delta = 5\%$) as acceptable in the MM group ($R_{26}^{MM} = 0.10$). Therefore, from equation ① $R_1^{N95} = 0.00197$ and $R_1^{MM} = 0.00404$; and in turn $R_{10}^{N95} = 0.0195$ and $R_{10}^{MM} = 0.0397$. Taking the difference, the value of Δ as prespecified thus equates to 2.02% for a 10-week study. The reduction of the follow-up period without a compensatory reduction in Δ thus represents an enlargement of the risk increase held to be acceptable by a factor of approximately 2.5-fold.

Results

Results from the prespecified analyses

The registered study took place from 4 May 2020 to 22 May 2021. The dates are listed for "enrolment", but also specified under Loeb *et al* Fig. 1 to include follow up, implying the last data used was collected May 22nd, 2021. Findings from 300 participants were reported. It is unclear whether follow-up of all then-enrolled participants was completed. When the study was halted in the countries with registered sites, MM appeared likely to be substantially inferior, approximately doubling risk to participants.(Fig. 3) The reported ITT analyses (less stringent than the prespecified PP analyses that were omitted) of infections show 14/148 (9.46%) for MM vs 7/152 (4.61%) for N95, difference 4.85%, 95% CI two-sided (prespecified): [-0.92%, 10.63%]; one-sided [0.02%, ∞](more appropriate based on prior knowledge; notably showing MM provide inferior protection vs N95 that is both statistically and clinically significant)(58).

Assessment of data collected in the countries where all prespecified sites were located against the prespecified Δ with (2.02%) or without (5%) appropriate compensation for the reduced follow-up period is not consistent with the reported finding of noninferiority.

Results of alterations to trial sites

Enrolment began at unregistered sites in Pakistan on June 24th, 2021, and ran until December 18th, 2021, by which time data had been collected from a total of 486 participants across all three countries. The

approximate doubling of risk in the MM arm remained, with COVID infecting 17/240 (7.08%) in the MM arm, and 9/246 (3.66%) in the N95 arm – a difference of 3.42%, 95% CI [-0.58%, 7.43%].(58) At this time (day 594 of the trial period) recruitment of an additional 90 participants was required to reach the prespecified enrollment target (unchanged in the registry throughout the trial).

Enrolment then began at the unregistered sites in Egypt, with the trial period in that country starting December 19th, 2021 and ending 100 days later on March 29th, 2022. An additional 518 participants were enrolled over the following four weeks (allowing for 10 weeks of follow-up), accounting for 52% of total trial enrollment.(58) Baseline seropositivity in Egypt was 81.6% (MM) and 80.5% (N95). In the presence of widespread community transmission (where the assigned PPE was not worn) in the Omicron wave (**Fig. 1**)(87) and substantially different participant demographics and context, sites in Egypt accounted for 74% of all COVID cases, with 35 of 52 (67%) in the MM arm, and 38 of 47 (81%) in the N95 arm, burying the signal from previously collected data.(58)

Results after inclusion of data from countries that were not prespecified, assessed against the prespecified Δ with (2.02%) or without (5%) appropriate compensation for the reduced follow-up period, are not consistent with the reported finding of noninferiority.

The brief trial period in Egypt meant data collection there necessarily occurred largely simultaneously. Three quarters of infections in Egypt (and the majority in the entire trial) appear to have occurred within a few weeks around the onset of the Omicron wave (**Fig. 1**). The strikingly different proportional hazard recorded in Egypt calls into question the assumption of proportional hazards. While Loeb *et al* reported that “*The analysis fulfilled the Schoenfeld residual test for the assumption of proportional hazards in Cox analysis*”, this assessment employed stratification by health care facility. Of note, 21 of the 29 facilities were in countries that averaged less than one case per hospital in each arm.(58)

While COVID infection rates in Canada (6.1% MM / 2.2% N95) were substantially lower than in Egypt (13.6% MM / 14.6% N95), the secondary outcome of “work related absenteeism” (Supplement table 2)(63) was substantially higher in Canada (16.0% MM / 14.8% N95) than in Egypt (6.6% MM / 8.8% N95).

Results of alterations and omissions of analyses (PP, ITT etc)

The prespecified PP analysis yielded frequencies of 11.95% (MM) and 10.76% (N95), and a point estimate of the difference of 1.20%, with a 95% CI of [-3.01%, 5.41%] – note that the upper bound exceeds the authors’ prespecified 5% limit for accepting a finding of noninferiority. The modified ITT (**Fig. 2**) data from Figure 2 of the study(58) allows analysis against the prespecified criterion, yielding a point estimate of the difference between MM and N95 outcomes of 1.2%, with a 95% CI of [-2.50%, +4.88%]. A reference to this interval in one of the authors’ responses to post-publication criticisms confirm they were aware of it.(88) The upper bound of this interval is only marginally below their prespecified 5% threshold to reverse the finding of noninferiority. The commitment to report COVID cases from all participants regardless of follow-up length was not met. However, the prespecified 5% threshold would be exceeded in all instances where the missing data add one more COVID case to the MM arm than the N95 arm (a “Fragility Index”(89) of 1), or where at least four cases are added equally to both arms (**Fig. 4**). Recalling that obtaining the reported finding of noninferiority required both the inclusion of the unregistered sites as well as the unregistered alteration to the analysis, for completeness we also analysed what the

outcome would have been if all aspects of prespecified location and analysis had been adhered to in combination (PP analysis of data from Canada + Israel), which resulted in a point estimate of 6.57%, with a 95% CI of [-1.94%, 15.08%] – an upper bound just over triple the prespecified 5% threshold for acceptable inferior performance by MM (**Fig. 3A**).

ITT analysis of the published data from all sites using the prespecified criteria and inclusion of the missing data *most likely* results in a finding that is directly opposite to the outcome reported by the study team.

Using the combined data from all published sites, PP₈₀ infection frequencies were 11.61% (MM) and 10.38% (N95), with a point estimate of the difference at 1.23% and a 95% CI of [-2.85%, 5.32%]. While use of PP₈₀ in place of PP reduced the upper bound from 5.41% to 5.32%, it was not enough to bring it below the critical 5% boundary, resulting in the same finding that MM are not noninferior to N95 under the prespecified analysis. In summary: 1) the less stringent PP₈₀ was substituted for prespecified PP analysis shortly before data collection was complete; 2) PP₈₀ analysis comes closer to but does not deliver a finding of noninferiority under the originally specified 5% criterion; 3) both PP₈₀ and the prespecified PP analyses were omitted from the final publication; and 4) the publication omitted the full 10-week data previously committed to, and reported modified-ITT analysis only.

The reported finding of noninferiority is a product of changing approaches over the course of the study. Analysis of the published data from the prespecified sites using the prespecified criteria and PP approach results in a finding that is directly opposite to the outcome reported by the study team by a large margin.

Results of further enlargement of Δ

A second alteration redefining Δ as a doubling of risk further enlarged its value late in the trial period. The prespecified 5% increase in absolute risk over a 6-month period represents an absolute difference in incidence rates – the potential that over the trial period, MM could result in 5 excess COVID infections per 100 wearers preventable by N95s. In contrast, the altered Δ scales with the N95 rate (**Fig. 3**). At the 9.3% infection rate reported for the N95 arm overall, MM would be declared noninferior unless the upper bound of the 95% confidence interval for that group reached 18.6%. At the 14.6% rate seen in Egypt, MM performance would be deemed acceptable with an interval reaching 29.1%.

In combination, the alterations to Δ increased the excess risk the researchers were willing to accept on behalf of the population to which their results would be applied by a factor of just under 5-fold overall (and ~7.2 fold based on the results in Egypt).

Results of missing SGBA+ analysis

Examination of the data in the Participant Characteristics table of the Loeb study revealed a clear allocation bias, with a statistically significant correlation between male sex and being allocated to the N95 arm (136/497 MM, 169/507 N95, $\chi^2 \approx 4.23$, $p < 0.05$) (**Fig. 5A**), indicating a failure of randomization.

Male sex was overrepresented (and female sex under-represented) in the N95 arm in all countries (Fig. 5B), although in Pakistan (only) the difference was negligible (moving one male from N95 to MM there would be sufficient for parity).

Discussion

Methodological considerations

Essential information was not prespecified in the trial registry, and / or was modified after the trial was complete – defeating the purpose of trial registration. Inconsistencies around basic information such as the number and location of trial sites means it is not possible to be confident that reporting was not selective, and that all data from all sites were included (**Fig. 6**). The below analyses nevertheless give the authors the benefit of the doubt unless there is reason to believe otherwise.

Consistent with a similar trial by Loeb and colleagues(90) published in 2009, the study was proposed and recorded in the registry as an intermittent-use trial, with subjects donning N95s “...when providing care to or when within three feet of a patient with any febrile respiratory illness”. This is inconsistent with proper use of respirators,(57) as subjects would be exposed to bioaerosols emitted by the patient prior to and during donning of the N95s, as well as from any patients with asymptomatic COVID.

Incorporation of unmitigated bioaerosol exposures into a trial purporting to assess the efficacy of N95 to mitigate exposure to those same bioaerosols would be expected to strongly bias the trial towards a finding of noninferiority for MM. As there is no minimum time required for pathogen transmission via even brief exposure to infectious aerosols, there is no practical upper bound to the magnitude of this bias.

Post-hoc assertions that the trial was carried out with all subjects in the N95 arm wearing their PPE continuously are unsupported by evidence:

- The claim is not supported by prospectively registered information;(65–67)
- The claim is not consistent with the initial study protocol;(64)
- The study ended March 29th, 2022, yet the modified statistical analysis plan dated February 17th, 2022 and the modified protocol dated March 1st 2022(64) both specify that subgroup analyses would include sites with and without universal masking;
- Despite being fundamental to the interpretation of the trial results, no explicit claim that all participants wore their assigned mask/respirator continuously at all sites throughout the trial was made in the publication(**Fig. 6**);(58)
- The first unambiguous claim to that effect was made on December 14th, 2022, in response to post-publication criticism of the study;(91)
- Prior to the appearance of that claim, a colleague and collaborator(92) of the team defending the study publicly reported having personally confirmed with one of the authors and an unknown number of participants that participants in the N95 arm were permitted to wear medical masks to comply with continuous-wear policies;(93–96)

- The authors' justification for not reporting the change as a protocol modification is that it was merely a fortuitous artefact of local policies that happened to coincide across all sites in four countries across three continents over the span of two years;(97)
- As noted above, the trial was explicitly designed around an inappropriate intermittent-use protocol – a fatal flaw from which unregistered protocol modifications and coincidental universal use are claimed to have salvaged it. Retroactive insertion into the registry with back-dating to the beginning of the trial (a repudiation of the purpose of trial registration) does not provide the evidence such claims require.

Alterations of trial sites

Trial sites in Egypt accounted for over half of total participants and nearly three-quarters of total COVID infections, taking place during the Omicron wave (**Fig. 1**). As expected, participants reported much higher levels of community exposure in Egypt than at other sites (Loeb *et al* Supplement Table 9),(63) and real exposure levels would have been substantially under-counted due to asymptomatic transmission, and unrecognized exposure events such as entering a poorly ventilated room, elevator or bus shortly after an infected individual had left. Exposure in the community where no protection was provided represents the obvious and most likely source of infection.

Loeb *et al* report that at the start of the trial, ~80% of Egyptian participants were seropositive and ~50% had been vaccinated against COVID with Sinopharm or Sinovac vaccines – considered effective by the WHO. (58,82–85) This would be expected to reduce the number that were susceptible to infection during the trial, and increase the proportion of infections that were asymptomatic (which would not have been self-reported). While ~15% of participants in both arms self-reported symptoms that subsequently resulted in positive PCR tests,(58) seroconversion exceeded 40% in both arms in the subgroup where it could be assessed,(63) and false negatives mean the true incidence was likely higher. It appears likely that the majority of the pool of susceptible individuals was infected in the community, rendering hospital exposures irrelevant. This hypothesis is supported by the fact that the results from Egypt are inconsistent with data from all other sites (collected during periods of lower community transmission).

The authors claimed that the difference in relative protection provided by MM vs N95 in Egypt compared to the other countries “...does not seem to be explained by differences in baseline seropositivity...” on the basis of RT-PCR confirmed COVID levels among participants who were initially seronegative (Loeb *et al* Supplement Figure).(63) However this is not borne out by the data. A total of 73 of the 518 participants in Egypt tested positive for COVID by PCR (Loeb *et al* Fig. 2).(58) As 23 of these were within the subgroup of 76 participants who were initially seronegative (Loeb *et al* Supplement Figure),(63) the remaining 50 were necessarily in the remaining 442. At 30.2% the incidence of PCR-confirmed COVID within the initially seronegative group in Egypt (the group comparable to the participants in the countries listed in the trial registry) is thus nearly triple the 11.3% of the initially seropositive group (RR 2.675, 95% CI 1.741 – 4.111, $p < 0.0001$),(98) providing evidence to support the expectation of reduced susceptibility and/or symptoms (and therefore self-reporting) in seropositive populations.

This possibility was dismissed on the basis of post hoc subgroup analysis of self-reported recollection of community exposures (Supplement Table 3).(58) However this analysis has minimal evidentiary value given high rates of community exposure, the long residence time of infectious aerosols even after the departure of an infected individual, and the context of high seropositivity that might be expected to reduced symptom intensity and hence make community contacts less likely to be identified.

In the absence of meaningful evidence to the contrary, the results from Egypt must be assumed to be an artefact of the obvious and well-understood mechanism of uncontrolled community exposure. This expectation is reinforced by the fact that results from Egypt are inconsistent with those of all other countries in the study. Pooling of these data with earlier results is not justifiable, and effectively erases the findings from all sites in the only countries listed in the trial registry at any point prior to publication.

The reported finding of noninferiority is entirely an artefact of the data from sites in Egypt, and cannot be obtained without them even if we were to accept all other alterations to the trial as legitimate.

Unexpected patterns in the data

No aspect of this trial is more central to its value than the integrity of the data on COVID incidence among participants. Loeb and colleagues presented data on infections diagnosed by PCR (in their Fig. 2)(58), by seroconversion, and on the total number of participants diagnosed by either technique (both reported in their Supplement Table 2)(63). A strong positive correlation is expected between these outcomes, as PCR and seroconversion are different ways of investigating the same underlying event – while neither method is perfect, COVID infection is generally expected to be the cause of both positive PCR tests and seroconversion.(99) Unexpectedly, the data reported shows the opposite pattern: perfect exclusion.

Combining the data from both arms of the trial in Egypt, there were 518 participants in total, of whom 73 tested positive for COVID by PCR.(58) Of the subgroup of 76 participants who were initially seronegative, 33 displayed seroconversion, and the total number of laboratory confirmed infections (defined as “infection confirmed by either RT-PCR or by seroconversion”) in Egypt was reported as 106.(63) As this is exactly the total of PCR and seroconversion positive results (73 + 33 = 106), there were necessarily zero participants who tested positive in both. In place of the expected strong positive correlation, the data reported exhibits perfect exclusion.

A conservative estimate of the probability of this situation arising naturally can be calculated by ignoring the expected positive correlation and treating PCR and serology results as independent variables. Given a pool of 518 individuals containing 73 who are PCR+, the probability that a randomly selected subset of 33 (those identified via seroconversion) would include zero PCR+ individuals can be determined using the combination formula:

$$\binom{n}{r} = \frac{n!}{(n-r)! * r!}$$

There are $\binom{518}{33}$ ways to choose 33 individuals from the entire pool, and $\binom{445}{33}$ ways to choose that same number from the subset of PCR-negative individuals. The probability of the reported outcome occurring

naturally if there was no correlation between detection of a COVID infection by PCR and detection of a COVID infection by seroconversion is therefore:

$$\frac{\binom{445}{33}}{\binom{518}{33}} \cong 0.00558$$

Considering the expected positive relationship, the true probability would be substantially lower.

The pattern observed in the data reported by Loeb and colleagues appears highly unlikely ($p < 0.006$) to occur naturally in data collected as described in the publication.

Also of note: this unexpected pattern means that within the 76 initially seronegative participants, the 23 PCR positives (Loeb et al. Supplement Figure)(63) and 33 seroconversions are necessarily additive. Thus, 56 of the 76 (74%, 70.3% of MM and 76.9% of N95) met the criteria for lab-confirmed COVID infection.

Influence of alterations and omissions of analyses

The transition from the prespecified PP analysis to ITT, PP₈₀ and finally modified ITT only without the prespecified analyses is particularly relevant(72) given the high dropout rate in the study, which exceeded 13% overall, including >25% in Canada and >50% in Israel (calculated from the data in figures 2 and 4 of the paper).(58) These modifications had the effect of reducing both apparent incidence rates and the magnitude of differences between them (**Figs. 2,3**). Reporting analysis as ITT despite censoring data from a significant number of participants is a departure from the definition of the term, and has been described as a form of misrepresentation.(79)

Reporting modified ITT as ITT analysis and omission of the prespecified PP analysis biased the study towards a finding of noninferiority.

Influence of enlargement of Δ

The abbreviation of the follow-up period from the 6-month prespecified in the initial protocol and in the trial registry to 10 weeks, without a corresponding adjustment of the prespecified Δ , represented an effective enlargement of Δ by a factor of approximately 2.5. With scientific peer review already complete, it is not clear that ethics review processes would have identified the dramatic increase in risk asserted as acceptable by such a seemingly minor technical change. This is particularly concerning as the groups that were both the subjects of the research and most directly impacted by its intended application do not appear to have been adequately engaged in the process of setting even the original Δ value.(100)

The second enlargement of Δ , coming only a few weeks before the end of the two-year study period, is also highly significant. The change from a 5% absolute difference to a doubling necessarily enlarges the prespecified Δ wherever incidence of COVID in the N95 arm was greater than ~5%. Given explicit concerns in the field predating this trial that *"The flexibility of the designs carries a risk of manipulation... Δ can also be enlarged post hoc to disguise an initial finding that the new treatment was inferior..."*, (72) it is noteworthy that this last-minute alteration was made during the peak of the Omicron wave (**Fig 1**), of which the investigators would necessarily have been aware. To illustrate the importance of this alteration,

consider a subgroup analysis of the data from Egypt (which dominated the study outcome in any event). As noted above, the data reported by Loeb and colleagues indicates that in the face of widespread community exposure, over 75% of known-susceptible (initially seronegative) participants in the N95 arm were infected during 10 weeks or less of follow up. As a result, no matter how poorly medical masks performed in reality, a finding of noninferiority would have been the only mathematically possible outcome – entirely as an artefact of the unregistered alterations to the trial.

In violation of the good practice requirement that all pre-specified outcome analyses be reported,(73,101–103) they were omitted and only the enlarged Δ was considered in the authors' conclusion that MM are noninferior to N95 for prevention of COVID. Selective reporting of outcomes and analysis is recognized as a type of *"...specific intentional or unintentional reporting that fails to faithfully reflect the nature and range of findings and that could affect the impression the results produce in readers."*(79)

Consequences of omission of SGBA+ analyses

In addition to general considerations of equity for participants and those impacted by research findings, there are specific technical reasons why this analysis was essential in this context. While Loeb *et al* reported *"The primary outcome was confirmed COVID-19 on reverse transcriptase polymerase chain reaction (RT-PCR) test"*, it is more correctly described as self-reported COVID with PCR confirmation (see below). Sex is known to interact with COVID, with males on average experiencing more severe acute COVID(104,105) while females are at greater risk of long COVID.(106,107) This means any imbalance could bias the primary outcome of self-reported illness due to the increased likelihood that an infection of a male participant would be recognized and reported in comparison with a female participant. Balanced representation of female and male participants was thus not only essential for equity, but also for the validity and interpretability of the study.

With N95 recognized in pre-existing national standards as the minimum level of protection required against potential exposure to SARS-CoV-2-containing aerosols,(57) allocation to the N95 arm was beneficial. Across the study, female sex increased the risk of being allocated to the less protective MM (RR 1.158, 95% CI 1.003 – 1.338, $p < 0.05$).⁽⁹⁸⁾ While not statistically significant when broken out by country, this pattern was reflected in Canada (RR 1.204, 95% CI 0.854 – 1.697), Israel (RR 1.773, 95% CI 0.741 – 4.242), and Egypt (RR 1.193, 95% CI 0.970 – 1.467). The exception was Pakistan (RR 1.022, 95% CI 0.764 – 1.367), notably the only country where the senior member of the trial team was female (overall the subject population, largely nurses and personal support workers, was 70% female while the study team, largely senior infection control doctors, was 68% male). This failure of randomization led to a disparity in the level of protection provided to male and female participants.

Compounding this issue, presenteeism (attending work when sick) has been reported to be particularly prevalent among HCW, and significantly higher among female vs male nurses, including specifically in Egypt(108–110). The inconsistent relationship between COVID rates and work-related absenteeism in Canada vs Egypt noted above suggests that economic and social factors may have encouraged Egyptian participants (and women in particular) not to report symptoms and to attend work when ill.

The failure of randomization and resulting inequities would be expected to bias the trial towards a finding of noninferiority.

Participants could not be blinded to their allocation and the details necessary to assess whether there were adequate safeguards against subversion of randomization(111) were not reported in the publication.

Other considerations

The omission of site information from the published information and the trial registry is particularly relevant in Egypt, as only one of the six sites was equipped with an HVAC system (in contrast to 100% of sites elsewhere, per Supplement Table 11),(58) with the other five provided only with “...a combination of air conditioning and outdoor air”. Without further information this could mean simply openable windows and some recirculating air conditioners, which would tend to encourage closing of the windows while providing essentially no air cleaning – the worst combination possible in the presence of infectious aerosols. This would be expected to significantly increase the relative risk of infection inside the health care facilities over sites in the registered countries,(14) including in spaces such as break rooms and non-patient areas where workers might be expected to remove their mask or respirator. The range of ventilation rates from 15 air changes per hour in Canada to only natural ventilation at some Egyptian sites indicates substantially different transmission environments,(112) emphasizing both the lack of adequate bioengineering support as required under TCPS2-11B(113) and the inappropriateness of pooling data from such inconsistent sources.

Lack of adequate ventilation at the majority of sites in Egypt would be expected to bias the trial towards a finding of noninferiority.

While presented as “...reverse transcriptase polymerase chain reaction (RT-PCR)–confirmed COVID-19”,(58) the study’s primary outcome is in actuality self-reported symptomatic COVID-19 with PCR confirmation. Dependence on self-reporting means asymptomatic infections would not have been captured, artefactually reducing event counts in both arms. Baseline seropositivity of over 80% in Egypt would be anticipated to reduce severity of illness in comparison to first exposure, further reducing the accuracy of self-reporting. Varying isolation requirements for individuals testing positive for COVID and their family members, along with variations in income support (or the lack thereof) during those isolation periods likely resulted in substantial disincentives to self-report that varied significantly between sites and over time. The presenteeism noted above would be expected to have intersectional effects with both the disincentives to report, and with the failure of randomization that resulted in the imbalance between male and female participants we identified above.

Participants in the MM arm were allowed to wear N95 at any time based on point of care risk assessment.(58) Considering that the most COVID-cautious participants would have had both the greatest motivation to report and seek treatment for suspected infection; and to take advantage of the opportunity to wear N95 if assigned to the MM arm, it would be expected that these factors would interact to further artefactually reduce cases recorded in the MM arm.

The combination and intersection of disincentives to report, inconsistencies in use of assigned PPE, and failure of randomization resulting a gender-specific bias in allocation would be expected to bias the study towards a finding of noninferiority.

The authors report that the only N95 respirator used in Israel was the Makrite 9500,(63) multiple lots of which were the subject of recalls in at least Canada(114) (October 5th, 2020) and Australia(115) (December 20th, 2021) due to filtration failure, spanning a time period that includes the entirety of the study period in Israel (November 11th, 2020 to January 27th, 2021). While the publication claims all participants were fit-tested, no details or lot information are provided.

Any failures of quality control and / or fit-testing procedures would be expected to bias the trial towards a finding of noninferiority.

Unreported conflicts of interest

As discussed above, COVID is known to be substantially airborne, transmitted in infectious bioaerosols.(3) Anticipated in the earliest days of the pandemic, this danger was overlooked by policy makers at great cost(2) - a “...very big mistake” where better decisions “...would have saved an enormous number of lives”.(116) Seven million deaths have now been officially attributed directly to COVID, with the real total estimated at 27 million(117) and possibly much higher,(118) and millions more suffer long-term impacts from Post Covid Condition (PCC).(119–123)

Any individual who might be viewed as having participated in that mistake had a strong competing interest in the outcome of this trial. A study that reported a finding consistent with inferior performance of the medical masks substituted for N95 respirators (required under the applicable national standard and for compliance with the precautionary principle) could invoke significant institutional and personal risks for such individuals.(57,124–126)

Sixteen of the authors as well as two of the three members of the Data Safety and Monitoring Board (DSMB) hold Medical Director of Infection Control (MDIC) or similar positions at their respective institutions (Table 1). Of these, nine (including the DSMB Chair) are located in the province of Ontario, where in 2021 the Ontario Nurses’ Association requested judicial review of hospital infection control policies they asserted were dangerously inadequate in failing to provide for universal use of N95 respirators.(100,127) Similar positions regarding SARS-CoV-2 mitigations had been taken nationally as early as February 2020 by the Canadian Federation of Nurses’ Unions and the Canadian Labour Congress(128).

Team member Dr. Leis was MDIC at one of the institutions in question, but also acted as a nominally non-partisan expert witness opposing this request. Dr. Leis filed an affidavit prejudging the outcome of the N95 study, with letters of endorsement from 29 fellow MDIC physicians, including study team members Drs. Muller, Mertz, Downing and Chagla, as well as DSMB members Drs. Johnstone (chair) and Katz.(129) Dated April 19th-26th, 2021, the endorsement letters attested to the accuracy of Dr. Leis’ affidavit, which asserted: COVID transmission is primarily “droplet” (non-airborne); limiting use of N95 to specific cases

provided adequate protection; and that these assertions were established so conclusively as to meet the high bar of the precautionary principle.(127)

Endorsed shortly before the end of data collection for the Loeb trial in Canada, the affidavit also included the statement: “...our experience at my hospital and other healthcare facilities throughout Canada where use of medical mask and eye protection alone to care for an unmasked patient with unrecognized COVID-19, has not resulted in transmission to healthcare workers.”(127) It is unclear how the members of the DSMB reconciled endorsing this statement as accurate with the then-current trial data they were responsible for being aware of, showing multiple infections in healthcare workers wearing medical masks. We note that the DSMB Chair was relatively junior for a role that includes a requirement to override the Principal Investigator (in this case Dr. Loeb) and terminate the trial if necessary to protect participants. Dr. Johnstone completed her graduate training under Dr. Loeb’s supervision in 2014, less than six years before the start of the trial(130).

Senior author Dr. Conly chairs the WHO Infection Prevention and Control Research and Development Expert Group for COVID-19 (**WHO-C19-EG** – of which Dr. Loeb was also a member),(131) upon whose advice the WHO’s position on COVID prevention was largely based in the first year of the pandemic.(132) This group had publicly argued against the need to adopt “...the precautionary principle with consequent use of particulate respirators instead of medical masks as a component of PPE for routine care of COVID-19 patients...” in August 2020,(125) despite previously receiving direct warnings to the contrary from the world’s leading experts on the generation and behaviour of infectious bioaerosols.(2)

Significant directly relevant competing interests were not disclosed in the study publication.

Conclusions

A fatally flawed study

It was well-understood (and clearly laid out in national standards)(57) prior to this study that N95 respirators protect the wearer from aerosols, including those carrying pathogens such as SARS-CoV-2, and that these protections apply regardless of whether or not the wearer is part of a larger group. The lack of expertise of public health and infection control decision-makers in this area – and the need for them to work collaboratively with those who have this expertise – has been repeatedly identified in prominent inquiries into infection control failures across decades.(124,133,134) There is a legitimate role for studies of parameters such as comfort, leakage and durability of fit, to determine whether the specific makes and models of PPE provided in a given environment are adequate. However, rigorous direct quantitative methods(38,135) – incorporating randomization, controls, workplace testing etc. – are essential. (79,101–103,136,137)

No combined analysis of the data from Canada and Israel was presented, instead they were pooled with data from unregistered sites in a dramatically inconsistent context, obscuring their significance. These important outcomes were not only ignored, but were misrepresented as inappropriate subgroup analysis with no evidentiary value.(138) The results from the registered study sites in Canada and Israel reflect

the well-established understanding that appropriate PPE can provide significant protection when worn during a substantial fraction of exposures to an airborne pathogen.

With exposure primarily in the workplace, the MM group was subjected to approximately a two-fold increase in detected COVID infections, despite poorly structured protocols for N95 use, inappropriate communication regarding their use in the study, and other implementation flaws. The superficially contradictory outcomes at the unregistered study sites in Egypt in the context of widespread community transmission reflect the obvious fact that PPE does not provide protection from an exposure that occurs while it is not being worn. This effect may not be attributed to failures of compliance on the part of participants, who were not provided with PPE or instructions to wear it in the community. To claim that this calls into question the ability of appropriate PPE to provide population-level protection against airborne infection is equivalent to building a dam across a small part of a major river and then claiming the results call into question whether dams can control the flow of water.

Sex and gender bias in research has been explicitly identified as a matter of fundamental justice by CIHR, requiring that the benefits and burdens of research be distributed equitably.(75) As noted above, the fact that N95 provide superior protection against potentially pathogenic aerosols was sufficiently well-established to be incorporated into national standards prior to the commencement of the study.(57) The statistically significant sex bias in allocation raises the question of whether some male participants may have been able to subvert randomization and ensure their placement in the lower-risk arm of the trial, displacing female participants into the higher-risk MM arm. With the study taking place in facilities where the study team, support staff and participants worked, the impacts of pre-existing social and/or power relationships must be considered.

There are thus three significant failures here: **Firstly, the risk to participants was not equitably distributed by sex (gender), a serious ethical failure.** Women were substantially more likely to be allocated less-effective(57) MM than N95 in every country with the exception of Pakistan - the lone country where the senior investigator was a woman. **Secondly, there was a failure of randomization with regards to a factor well known to interact significantly with the primary outcome, calling into question the validity of the entire study.** Without details of the allocation process it is not possible to assess the source of this failure, and whether adequate precautions were taken against failure / subversion at the allocation stage. The well-known example of large-scale Canadian mammography trials provides an example of the damage that can be done by subversion of randomization even at relatively low levels.(111) **Thirdly, there was a failure to directly address these initial failures in the publication.** Research on human subjects – particularly research involving substantial risk of serious harm to both participants and those impacted by any errors in the research findings, as was the case here – carries with it an obligation to be thorough, and an obligation to be transparent.

When the study was terminated at all sites in the prospectively registered countries, the results showed clear evidence of a result opposite to the primary published finding, showing medical masks very likely provided substantially reduced protection against a pathogen with potential to cause death or serious harm. This imposed obligations (including to participants) under TCPS2(139–141) and

international norms(142) that were not met. It also appears inconsistent with assurances provided by team members to a judicial review process requested by the Ontario Nurses Association.(127)

In summary, we find that the trial by Loeb and colleagues(58) was poorly designed, poorly implemented, and the results misinterpreted. **The data reported exhibit patterns unlikely to occur naturally.** Randomization of participants appears compromised on at least the basis of participant sex, with a statistically significant preference for allocating the more protective N95 required by the relevant national standard(57) to men, and the MM which do not satisfy those requirements to women. (57) **Unexplained differences remain between the prospectively recorded study protocol, the way the study was represented by the authors, and what appears to have actually taken place.** The effects of the trial's many shortcomings were not evenly distributed but consistently biased the trial towards a finding that MM were noninferior to N95. While widely publicized by the authors(61,62) and already being encoded into nominally authoritative infection control literature(59,143,144) and practice,(60,145) **the primary finding was obtained only via multiple significant alterations to the conduct, analysis and criteria of the trial, none of which were prespecified in the trial registry.** In at least the majority of cases the impacts of those alterations were predictable by the Trial Steering Committee at the time they were made. Even without considering biases towards a finding of noninferiority, the unreported prespecified PP analysis with 5% noninferiority margin is by itself sufficient to reverse the reported outcome. Finally, **unexpected patterns in the data require further investigation.**

The claim that this study shows medical masks are noninferior to N95 for protection against COVID infection is therefore invalidated, and there is ample basis to require a complete retraction of the study.

As a result of the major flaws noted above, the following actions are urgently required:

1. Annals of Internal Medicine should immediately retract the publication by Loeb *et al.*,(58) assess why its flaws were not identified in AIM's Fast-Track Review process, and revisit the journal's compliance with ICMJE Recommendations.
2. All institutions that provided ethics approval should identify and implement the changes required to prevent the failures identified here from recurring. Particularly serious concerns include the absence of the worker safety expertise specifically identified as essential by the SARS Commission(133) in the design of the study, and in the membership of the TSC and DSMB; non-compliance with CAN/CSA-Z94.4;(57) the repeated expansion of risk accepted by the TSC and what ethics oversight was involved (including whether the technical information around increase in risk was adequately conveyed); failure to address risk to (and obtain consent from) patients under the care of participants in the study; failure to address sex and gender considerations and their intersection with the power imbalance between the study team and participants who were also under their authority; failure of the study team to identify and mitigate the gender imbalance that both increased risk for female participants and would be enough to call the study results into question on its own; failure of the DSMB to act to protect the health and safety of participants.
3. Organizations and processes citing the reported findings of the Loeb study(58) as evidence should revise their characterization of this trial as an RCT with pre-specified endpoints, re-evaluate the gaps in understanding that allowed its inclusion, and draw more effectively on the substantial body of

evidence for the relative efficacy of respirators for airborne pathogens.(146) This includes WHO guidelines on infection prevention and control(144) and suggestions on revised terminology around airborne infectious diseases(147,148), and similar processes elsewhere.(60,145)

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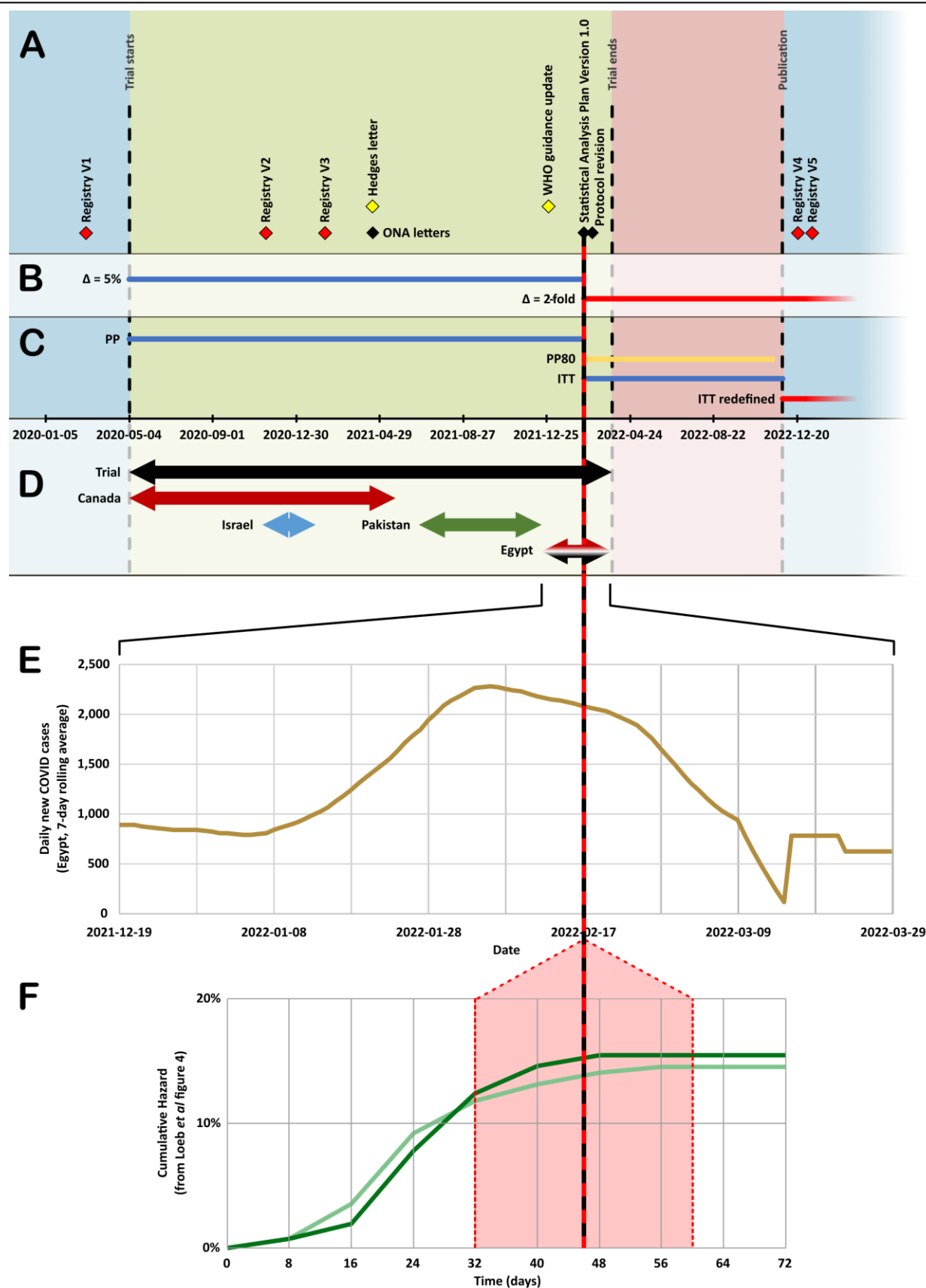
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Figures

Figure 1 (following page): Timeline of key events and alterations to the study. The trial took place from May 4th, 2020 to March 29th, 2022 across multiple countries. The exact number of sites is unclear. Key events (A) include a Statistical Analysis Plan (black and red vertical line, identified as Version 1.0 and dated February 17th 2022), which introduced a number of major changes after 95% of the trial period was complete. While this alteration was not prospectively registered, the trial registry was modified several times, in some cases retroactively after publication (red diamonds). Twelve sites in Canada and one in Israel were prospectively included in the trial registry. No sites were prospectively registered in Pakistan or Egypt, although one site in each was retroactively added to the registry after publication. The main text of the paper refers to 17 sites in Canada, 2 in Israel, 4 in Pakistan and 6 in Egypt, while Supplement Tables 10 and 12 refer to 23 sites in Canada and 11 “study units” in Pakistan. Assuming no sites were excluded entirely *post hoc*, there appear to be between 29 and 42 in total. A warning letter from Hedges *et al* dated April 19th, 2021 (yellow diamond) explicitly raised several issues including unnecessary risk to participants and the need to terminate the study and report the results. The data collected at this time was consistent with substantially inferior performance of medical masks and elevated risk to participants in that arm of the study. While the study was ended at the last of the registered sites shortly afterwards (D), it was then moved overseas to Pakistan and subsequently to Egypt. Five out of six sites in Egypt lacked mechanical ventilation, a critical shortcoming as the WHO had released guidance December 22nd, 2021 (yellow diamond) stating explicitly that all HCW should wear a respirator (N95 or equivalent) when caring for patients with known or suspected COVID where ventilation is poor or cannot be assessed. The modifications made February 17th 2022 included dramatically increasing the level of increased risk (see below) the study team was willing to accept as “noninferior” on behalf of participants (B) and redefinition of the term “per protocol” (PP) to include participants who completed 80% of the follow-up (PP₈₀) (C). While PP analysis was prespecified, and either PP or PP₈₀ analysis of the published data with the prespecified 5% criterion fails to reproduce the published finding that MM are noninferior, both were omitted *post hoc*. The intention to treat (ITT) analysis introduced at the same time as the PP redefinition was itself modified (ITT_{mod}) at publication. The major alterations (black and red vertical line) which facilitated a finding of noninferiority at elevated COVID rates (see below) were made in the midst of elevated COVID rates during Egypt’s Omicron wave (E – data from the WHO COVID-19 dashboard), which the study team would likely have been aware of. While the trial data is presented only in aggregate form, the limited (100-day) trial period in Egypt constrains when it would have been possible to collect the 72 days of data reported (F – extracted from Loeb *et al* Figure 4). The alterations took place on the 60th day of that period, meaning any given participant in Egypt would necessarily have been between day 32 and 60 of their follow-up period (pink band). Therefore data collection was almost entirely complete at that time. The major increase in the Δ value thus took place exactly when such a change became essential for the study to produce a finding that medical masks were noninferior to N95. A close examination of the information accessed by the DSMB, TSC, and any Contract Research Organizations involved in the trial in Egypt regarding the nominally concealed findings of the study at that time is imperative.



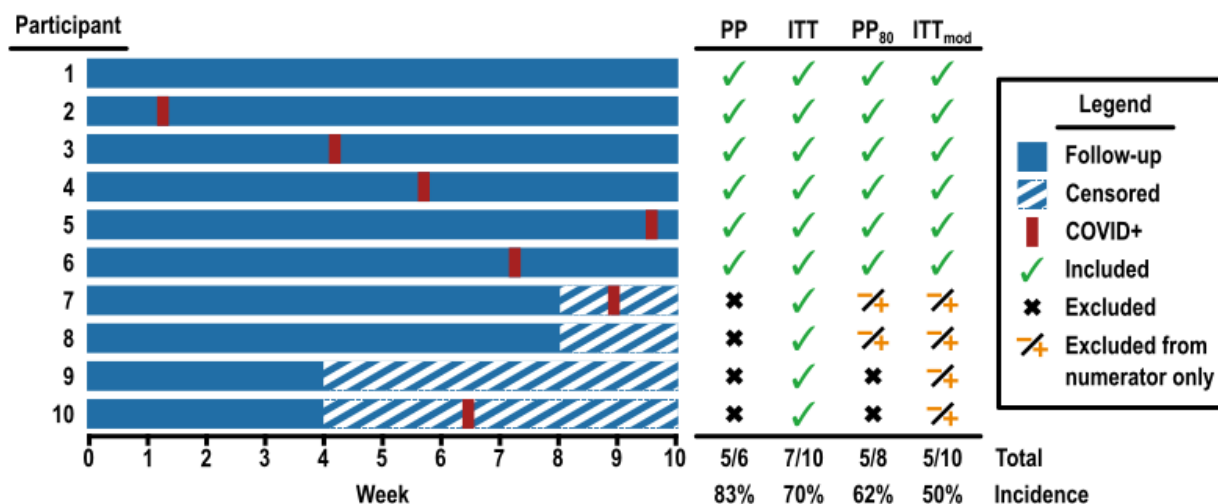


Figure 2: Changes in data inclusion criteria can be used to affect outcomes. An illustrative theoretical example of ten participants shows the impact of alterations to analysis methods. Participants followed for the entire 10 weeks are shown in blue. The bar becomes hatched where a participant is censored due to a protocol violation (in the Loeb study, receipt of an effective vaccine). Red bars represent a positive COVID diagnosis. Note that a proportionate reduction in cases reported in both the MM and N95 arms would reduce the difference between them, facilitating a finding of noninferiority. Per Protocol (PP) analysis was prespecified, where only participants who followed the protocol exactly are counted. In this theoretical example, PP analysis excludes 4 participants, producing a result of 5/6 COVID positive. Intention To Treat (ITT) analysis includes all data from all participants. COVID incidence might be expected to be reduced post-vaccination but any cases should still be recorded. In this example, 7/10 participants were positive. The novel approach of redefining PP to include participants censored after 80% of the prespecified follow-up period (which we refer to as PP₈₀ to avoid confusion with true PP analysis) has the effect of incorporating those patients into the denominator, but omitting any cases among them from the numerator, yielding a reported incidence of 5/8. Finally, the redefinition of ITT analysis at the time of publication (which we have termed ITT_{mod} to avoid confusion with true ITT) includes all participants in the denominator, but excludes any post-censorship cases from the numerator (despite the commitment in the final protocol update to record them), yielding a reported incidence of 5/10.

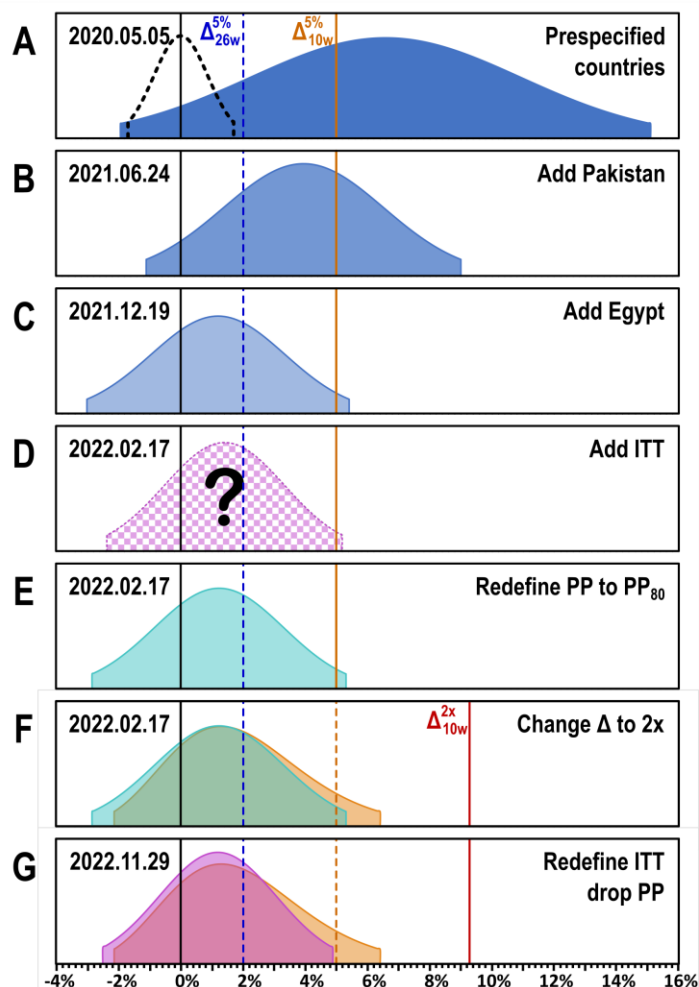


Figure 3: Alterations to the registered trial determined the reported outcome. Estimates of the difference in incidence between the N95 and MM groups, plotted for simplicity as normal distributions using 95% confidence intervals calculated from the data in the study publication, truncated to indicate the bounds of the 95% CI. The hypothesis that there was no difference in protection provided by medical masks vs N95 anticipates a distribution centred on the **black line** at 0 (**dashed black line**). A shift to the right would result if N95 provide better protection (as is expected for an aerosol hazard). The claim that medical masks are noninferior to N95 requires that the upper bound of the 95% CI (right end of the distribution) fall below (to the left of) the noninferiority line (Δ : **blue** – prespecified 5% over 26 weeks; **orange** – 5% over 10 weeks; **red** – 2x over 10 weeks). Dates indicate when changes that produced a given outcome were applied. Results from the prespecified countries and analysis method (PP) are shown in (A). Subsequent alterations including addition of sites in Pakistan (B) and Egypt (C), addition of ITT (D – imputed from censored participants as the planned 10-week data was omitted from the publication) and redefinition of PP to PP₈₀ (E) still produced a finding (medical masks not noninferior to N95) opposite to what was reported. Note any unreported cases in the censored PP₈₀ data would shift the curve further to the right. Changing to an Odds Ratio approach (orange curve) and enlarging the value of Δ (F) ultimately delivered the reported result of noninferiority. ITT was redefined to ITT_{mod}, excluding the full 10-week follow up (G), which was omitted from the publication along with both the prespecified PP and modified PP₈₀ analysis. Notably, analysis of the data from prespecified countries using the prespecified approach (A) reverses the outcome despite all enlargements of Δ .

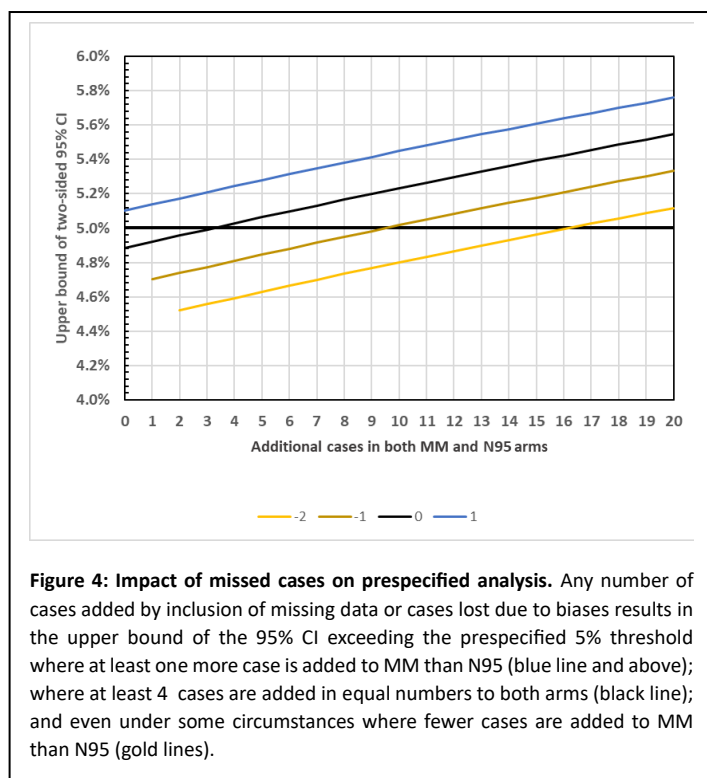
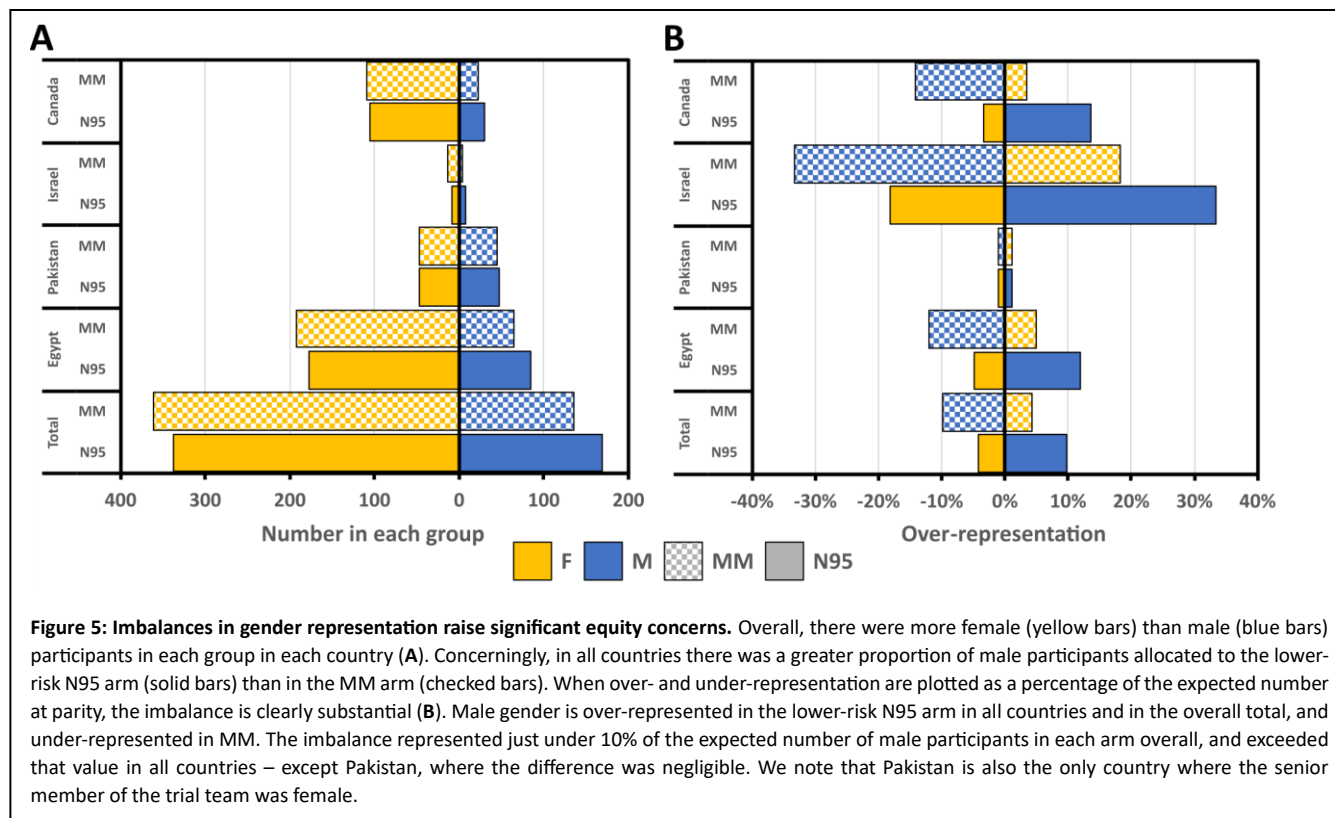
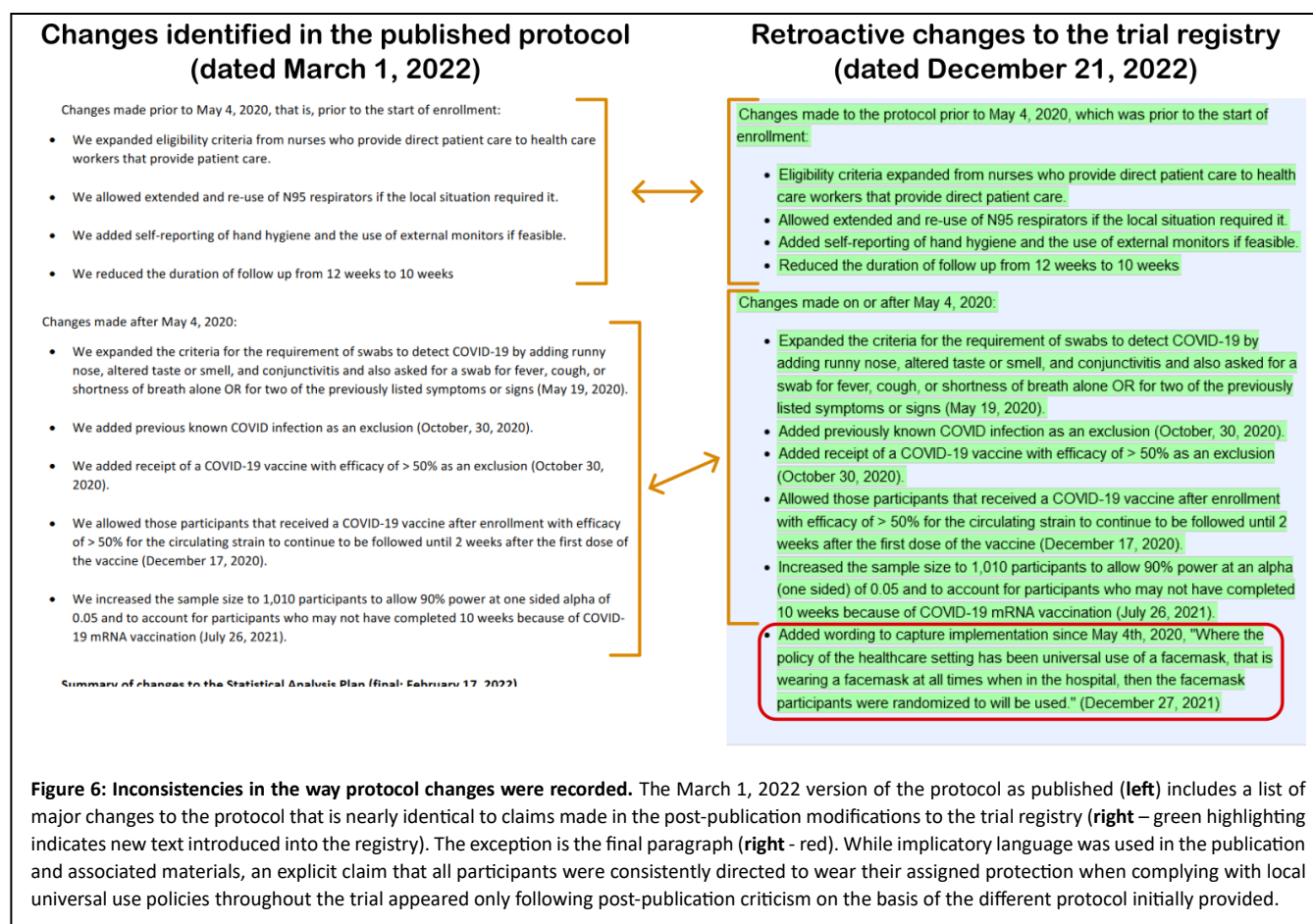


Figure 4: Impact of missed cases on prespecified analysis. Any number of cases added by inclusion of missing data or cases lost due to biases results in the upper bound of the 95% CI exceeding the prespecified 5% threshold where at least one more case is added to MM than N95 (blue line and above); where at least 4 cases are added in equal numbers to both arms (black line); and even under some circumstances where fewer cases are added to MM than N95 (gold lines).





Name	Advanced Training?				Study leadership?	Interest in a finding of noninferiority	Study investigator?
	Clinical	Stats / Epi / Trial	Mechanistic science	OH&S / PPE			
Ali, K	MD	No	No	No	Niagara Health Services	MDIC Niagara Health Services	ON
Bartholomew, A	RN	MSc(N)	No	No			
Borhan, S	No	PhD (HRM)	No	No			
Castellucci, L	MD	MSc (CE)	No	No	Ottawa Hospital		ON
Chagla, Z	MD	No	MSc (ID)	No	St. Joseph's Healthcare	MDIC St. Joseph's Healthcare; ONA Affidavit	ON
Cividino, M	MD	No	No	DOHS, CCBOM		IPAC Physician with Public Health Ontario	ON
Conly, J	MD	No	No	No	Foothills Medical Centre; TSC	MDIC Alberta Health Services (Calgary Zone); Foothills Medical Centre; Chair, WHO C19 EG	AB
Downing, M	MD	No	No	No	St. Joe's Unity Health	AMDIC, Unity Health, Toronto; ONA Affidavit	ON
Frenette, C	MD	No	No	No	Montreal University Health Centre	MDIC McGill University Health Centre	QC
Glavin, V	MD	No	No	No	Brantford General Hospital		ON
Hashmi, M	MD	No	No	No	TSC		Pakistan
Hassany, M	MD	MSc (?)*	No	No			Egypt
Hookoom, R	No	No	No	BASc, eMBA			
Kim, J	MD	No	No	No		MDIC Rockyview General Hospital	AB
Kinross, J	MD	No	No	No			
Larios, O	MD	No	No	No		Senor MDIC Alberta Health Services (province-wide, acting); South Health Campus	AB
Leis, J	MD	MSc (QIPS)	No	No		MDIC Sunnybrook Health Sciences Centre; ONA Affidavit**	
Loeb, M	MD	MSc (?)*	No	No	Trial PI; TSC	MDIC Hamilton Health Sciences	ON
Mansour, S	MD	No	No	No	Hopital Montfort		ON
Mertz, D	MD	MSc (HRM)	No	No	Hamilton Health Sciences	MDIC Hamilton Health Sciences; ONA Affidavit	ON
Missaghi, B	MD	No	No	No		MDIC Peter Loughheed Cancer Centre	AB
Muller, M	MD	PhD (CE)	No	No	St. Mike's Unity Health	MDIC Unity Health; Chair, Ontario PIDAC-IPC Committee; ONA Affidavit	ON
Newton, J	No	No	No	No			
Parkes, L	MD	No	No	No	The Jewish General Hospital	MDIC CIUSSS du Centre-Ouest-de-l'Île-de-Montréal	QC
Pullenayegum, E	No	PhD (Biostats)	No	No	TSC		ON
Singh, P	No	No	No	No			
Smith, S	MD	MSc (CE)	No	No	University of Alberta Hospital	MDIC University of Alberta Hospital	AB
Somayaji, R	MD	MPH	No	No			AB
Tarhuni, W	MD	No	No	No	TSC		Egypt
Vayalunkal, J	MD	No	No	No			AB
Youngster, I	MD	No	MMSc	No	Golden Care Long-Term Care Facility		Israel
DSMB members							
Johnstone, J	MD	PhD (HRM)	No	No	DSMB	MDIC Sinai Health; Former Loeb graduate student; ONA Affidavit	
Katz, K	MD	MSc (LMP)	No	No	DSMB	MDIC North York General Hospital; ONA Affidavit	
Koval, J	No	PhD (SAS)	No	No	DSMB		

Table 1: Study authors, training, competing interests, and study involvement.

Abbreviations (A)MDIC: (Associate) Medical Director of Infection Control or similar position with authority and responsibility for workplace safety and PPE decisions; AB, Alberta; BASc: Bachelor of Applied Science; CCBOM: Certificat of the Canadian Board of Occupational Medicine; CE: Clinical Epidemiology; DOHS: Diploma in Occupational Health and Safety; DSMB: Data Safety and Monitoring Board; eMBA: Executive Master of Business Administration; HRM: Health Research Methodology; ID: Infectious Diseases; IPAC: Infection Prevention and Control; LMP: Laboratory Medicine and Pathology; MD: Medical Doctor; MPH: Master in Public Health; MSc: Master of Medical Sciences; MSc: Master of Science; N: Nursing; ON: Ontario; PhD: Doctor of Philosophy; PI: Principal Investigator; QC: Quebec; QIPS: Quality Improvement and Patient Safety; RN: Registered Nurse; SAS: Statistical and Actuarial Sciences; TSC: Trial Steering Committee; *We were unable to identify the details of the MSc held by Drs. Loeb (assumed to be non-thesis as no mention was found in the MacSphere database) and Hassany (numerous records found under that name). **Refers to the April 2021 Affidavit declaring COVID transmission was known not to be airborne with sufficient certainty to meet the requirements of the precautionary principle, written by Dr. Leis and endorsed by 29 colleagues.